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| 10/539,446 | 06/20/2005 | Zhiwen Zhou | | 8654 |

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| EXAMINER | |
|---|---|
| ZARA, JANE J | |
| ART UNIT | PAPER NUMBER |
| 1635 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/539,446 | ZHOU ET AL. | |
| | Examiner | Art Unit | |
| | Jane Zara | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

This Office action is in response to the communication filed 6-23-08.

Claims 1-7, 9-12 are pending in the instant application.

***Election/Restrictions***

Applicant's election with traverse of SEQ ID No. 3 in the reply filed on 6-23-08 is acknowledged. The traversal is on the ground(s) that all of the sequences claimed are derived from the gag-pol of HIV and thus are not patentably distinct, that searching all of them would not pose an undue burden on the Examiner. Applicant also argues that all of the sequences and methods using them that are instantly claimed have been found to have unity of invention, as illustrated in the EPO search report. This is not found persuasive because, pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the different amino acids and nucleic acid molecules listed in claims 1 and 3, and encompassed by claims 1-7, and 9-12, are subject to restriction in domestic applications. In the instant case, one independent and distinct nucleotide or amino acid sequence is examined in a single application without restriction. Those sequences which are patentably indistinct from the sequence or region selected by the applicant will also be examined. Since claims 1-7, and 9-12 specifically embrace different polynucleotides with different SEQ ID Nos., and since each of these polynucleotides is considered to be structurally independent, because each is represented by a unique nucleotide sequence, they are properly considered separate inventions. Furthermore, a search of all the sequences

claimed presents an undue burden on the Patent and Trademark Office to search and examine.

The requirement is still deemed proper and is therefore made FINAL.

SEQ ID NOs. other than SEQ ID NO. 3 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6-23-08.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozal et al (USPN 5,631,128) and Pavlakis et al (USPN 5,965,726), and Kraus et al (USPN 5,958,768), the combination further in view of Fire et al (USPN 6,506,559) and Schwarz et al (Cell, Vol. 115, pages 199-208, 2003).

The claims are drawn to compositions and methods of treating and/or preventing HIV infection comprising the administration, to eukaryotic cells, of a composition comprising single stranded (antisense or ribozymes) or double stranded (RNAi) RNA molecules that comprise all or a fragment of between 19 and 28 nucleotides of SEQ ID NO. 3, and which RNAi molecules optionally further comprise two uracil nucleotides at either the 5' or 3' termini, comprise a hairpin RNA consisting of a stem part and a loop part, and which loop part is non-complementary and is a spacer between the self-complementary portions of the RNAi molecule, and which compositions optionally additionally comprise an expression vector that expresses the single or double stranded molecules, and liposomes for delivery of the RNA molecules to a target cell.

Kozal et al (USPN 5,631,128) teach single stranded oligonucleotides that specifically target the nucleic acid sequence encoding gag of HIV, including a 29 nucleotide fragment of SEQ ID NO. 3 (see SEQ ID NO. 3 of Kozal, and the alignment of nucleotides 11-39 of SEQ ID NO. 3 of Kozal with nucleotides 1-29 of SEQ ID No. 3 of the instantly claimed invention).

Pavlakis et al (USPN 5,965,726) teach single stranded oligonucleotides that specifically target the nucleic acid sequence encoding gag of HIV, including a 29 nucleotide fragment of SEQ ID NO. 3. Pavlakis also teaches the use of liposomal

compositions for enhancing delivery and uptake by target cells of nucleic acids (see SEQ ID NO. 28 of Pavlakis, and the alignment of nucleotides 5-33 of SEQ ID NO. 28 of Pavlakis et al with nucleotides 1-29 of SEQ ID No. 3 of the instantly claimed invention; see also example 5, col. 49).

Kraus et al (USPN 5,958,768) teach the use of nucleic acid constructs comprising DNA or RNA and encoding antisense and ribozymes for specifically targeting and inhibiting the expression of HIV, for inhibiting HIV replication and for treating HIV infections (see col. 1-3; col. 6-7; col. 9; col. 11; claims 1, 5, 11).

The primary references of Kozal et al, Pavlakis et al, and Kraus et al do not teach an siRNA molecule comprising fragments of between 19-28 nucleobases of SEQ ID NO. 3 and its complement in a hairpin conformation and further comprising uracil dinucleotide overhangs at either the 5' or 3' termini.

Fire et al (USPN 6,506,559) teaches the design and use of siRNA molecules for inhibiting the expression of a target gene of known sequence. Fire teaches siRNA molecules that are optionally two separate, self-complementary strands or a single, self-complementary strand which comprises a non-complementary loop joining the self-complementary regions to form a hairpin RNA in the siRNA molecule (see col. 1-5; 7; claims 1, 5, 6, 10 and 11).

Schwarz et al (Cell, Vol. 115, pages 199-208, 2003) teach the optimization of siRNA molecules comprising fragments between 19 and 28 nucleobases for targeting and inhibiting expression of a target gene sequence, including adding dinucleotide overhangs to the 5' or 3' termini of the siRNA molecules, including two uracil

nucleotides (see the entire article, esp. pages 199-200, and figures 3 and 4 on pages 204 and 205).

It would have been obvious to one of ordinary skill in the art to design and optimize siRNA molecules comprising a fragment of between 19-28 nucleobases of SEQ ID NO. 3 to target and inhibit the expression of HIV because the target region of HIV encoded by SEQ ID NO. 3 was well known in the art at the time the instant invention was made, and was well known as a target region of HIV that was susceptible to antisense or probe binding, as taught previously by both Kozal and Pavlakis, and siRNA molecules were also well known in the art to be effective for targeting and inhibiting expression of known target genes, as taught previously by both Fire and Kraus.

One of ordinary skill would have been motivated to use siRNA molecules comprising between 19 and 28 bases of SEQ ID NO. 3 for treating HIV infections because the optimum lengths of siRNA molecules were taught previously by many in the art, including Fire and Kraus, and SEQ ID No. 3 was a well known target site of HIV, as previously taught by Kozal and Pavlakis. One would have been motivated to use siRNA molecules as therapeutic agents to treat HIV because target gene inhibition using inhibitory oligonucleotides was a well known technique to use for HIV therapy, as illustrated in the teachings of Kraus, and Fire points out the advantages of siRNA compared to ribozymes, triplexes and antisense in inhibiting target gene expression.

One would have been motivated to place dinucleotide overhangs, including uracil dinucleotide overhangs, on siRNA constructs because Schwartz taught the advantages

of such terminal overhangs for efficient RISC complex formation using siRNA. One of ordinary skill would have reasonably expected that siRNA comprising 19-28 nucleobase fragments of SEQ ID NO. 3 would successfully target and inhibit the expression of HIV because this region was well known as an important region (e.g. gag-pol) for viral replication, and this region was well known as an accessible target region for probe or antisense binding. One of ordinary skill would have reasonably expected also that a single, self-complementary strand encoding an siRNA would self assemble into a hairpin structure comprising the siRNA molecule because these single self-complementary siRNA had been taught previously by Fire et al and one would have been motivated to design these for ease in assembly of the a single strand, rather than assembly of two separate strands in a cell. One of ordinary skill would have also reasonably expected that liposomal compositions comprising the instantly claimed siRNA molecules would provide for enhanced target cell delivery and offer viable therapeutic candidates for treating HIV infections.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the

Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Jane Zara**
**9-4-08**

/Jane Zara/

Primary Examiner, Art Unit 1635